Bleomycin A5 sclerotherapy for cervicofacial lymphatic malformations

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Objectives: **The purpose of this study was to document the results of bleomycin A5 sclerotherapy for cervicofacial lymphatic malformations (LMs), and the clinical data of 65 patients between October 2004 and October 2007 were reviewed.**

Methods: **Of the 65 patients in the study, 60 patients were given intralesional injection of bleomycin A5. Five patients underwent partial resection, and then an injection of bleomycin A5 for the remaining lesion. The outcomes were assessed by physical examination and Doppler ultrasonography scan. The follow-up time was from 6 months to 3 years after the last injection (mean, 16 months).**

Results: **Among the 65 patients, 41 were men and 24 were women (1.7:1 male:female ratio), the age range was 3 months to 45 years (mean, 12 years). Thirty-two lesions (49%) were macrocystic, 30 (46%) were microcystic, and 3 (5%) were combined. Each patient received 1 to 10 injections (mean, 3.0 injections) for the whole course of treatment, and the total dose of bleomycin A5 was from 8 to 80 milligrams (mean, 24.0 mg). Twenty-six of 32 macrocystic lesions (81%) showed greater than 90% reduction, whereas another 6 (19%) exhibited 50% to 90% reduction. Nineteen of 30 microcystic lesions (63%) showed greater than 90% reduction; 10 (33%) had 50% to 90% reduction; and 1 (4%) had less than 50% size reduction. Of the 3 combined lesions, 2 (67%) had greater than 90% shrinkage, and 1 (3%) had less than 50% reduction. The complications included ulceration of oral mucosa, minor soft tissue atrophy, mild fever, and hematoma. There was no recurrence throughout the follow-up period.**

Conclusion: **These data suggest bleomycin A5 is a safe and effective intralesional agent for the treatment of macrocystic LMs, superficial oral mucosa LM, and localized deep microcystic lesions. For extensive macrocystic LMs involving contiguous anatomic areas and diffuse microcystic lesions involving deep tissues, bleomycin A5 injection combined with resection is necessary. (J Vasc Surg 2011;53:150-5.)**

Lymphatic malformations (LMs) are developmental anomalies consisting of abnormally formed lymphatic channels and cystic spaces of varying size. Histologically, the vascular spaces are filled with eosinophilic, protein-rich fluid. A single layer of flattened endothelium lines the channels and the walls are composed of abnormally formed smooth and skeletal muscular elements.[1] There are three morphologic types of LMs: microcystic, macrocystic, and combined (combination of microcystic and macrocystic components). Macrocystic LMs are comprised of single or multiloculated cysts that vary in size and are filled with lymphatic fluid; they manifest as soft, compressible or noncompressible, translucent masses. Microcystic LMs are comprised of abnormal lymphatic tissue with a variable fibrous/fatty component, tiny cysts, or ectatic channels.[2]

More than 70% of LMs are located in the head and neck. These cervicofacial lesions can involve oral mucosa, skin, subcutaneous tissue, muscles, and the maxillofacial bones. LMs cause pain, bleeding, infection, muscular atrophy, malocclusion, speech difficulties, feeding problems, airway obstruction, and cosmetic deformities. Spontaneous regression of LMs sometimes occurs, typically as macrocystic lesions in the posterior cervical triangle.[3]

Several methods have been used to treat LMs, including surgical excision,[4-6] sclerotherapy,[7] laser therapy,[8,9] and radiofrequency ablation.[10,11] Resection is the traditional method; however, complete excision is usually not possible. Infiltration into adjacent tissue and incomplete resection result in a high recurrence rate. There are also postoperative complications, such as inadvertent nerve injury, airway obstruction caused by swelling, hematoma formation, wound infection, and hypertrophic scarring. Because of the relatively high morbidity associated with resection, sclerotherapy has assumed a more prominent role in recent years. A variety of sclerosing agents have been used, including OK-432, bleomycin, doxycycline, sodium tetradecyl sulfate 3%, ethanol, alcoholic solution of zein, fibrin sealant, polidocanol, sodium morrhuate, and acetic acid.[2,12-19]

Bleomycin was first developed as an antineoplastic antibiotic in 1966[20]; its mechanism of action is inhibition of DNA synthesis[21]; its sclerosing effect was discovered later. The mechanism involves damage to endothelial cells with a nonspecific inflammatory reaction and occlusion of vessels. It was initially reported in 1977 for the treatment of cystic LMs by Yura et al.[14] They reported effective results in macrocystic LMs. In this study, we present our experience with bleomycin

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Table I. Anatomic location of macro and microcystic lymphatic malformations in 65 patients

Sites	*No. of patients (%)*
Local lesions	39
Oral mucosa	
Tongue	14 (21.5)
Buccal	2 (3.1)
Non-oral mucosa	
Parotideomasseteric	10 (15.4)
Neck	6 (9.2)
Submandibular	1 (1.5)
Cheek	4 (6.2)
Floor of mouth	2 (3.1)
Diffuse lesions	26
Oral mucosa/deep	
Cheek	4 (6.2)
Cheek/lip	3 (4.6)
Cheek/tongue	1 (1.5)
Multiple lesions	
Facial	3 (4.6)
Neck/parotid/submandibular	8 (12.3)
Facial/cervical	5 (7.7)
Multiple/bilateral	2 (3.1)

A5 (Pingyangmycin; Tianjin Taihe Pharmaceutical Co Ltd, Tianjin, China) sclerotherapy in the treatment of macrocystic, microcystic, and incompletely resected LMs.

METHODS

Sixty-five patients with LM in cervicofacial regions were treated between October 2004 and October 2007. The diagnosis was confirmed by reviewing each patient's medical history, conducting a physical examination, Doppler ultrasonography scan, and magnetic resonance imaging. LMs were classified as either macrocystic, microcystic, or combined (both macrocystic and microcystic components). The lesions were separated into local and diffuse categories based on the anatomic locations. We defined diffuse lesions as involving oral mucosa and deep tissues, and cervicofacial areas, unilateral or bilateral.

Sixty patients received only intralesional bleomycin A5. Five patients initially had partial resection, then injection of bleomycin A5 into residual lesions. For most patients, the procedure was performed routinely under regional anesthesia in the office therapeutic room. For others, the procedure was carried out under sedation or general anesthesia in the operating room. For macrocystic and cystic components of combined LMs, 8 mg bleomycin A5 powder was dissolved in 3 mL lidocaine (2%, 2 mL) and dexamethasone (5 mg, 1 mL). Injection was performed through a 21-gauge needle. After aspiration of lymphatic fluid, the needle was kept in place and the bleomycin A5 solution was injected into the cystic cavities. For the sclerosis of microcystic LMs involving oral mucosa or subcutaneous tissue, bleomycin A5 (8 mg) powder was dissolved in 3 to 5 mL lidocaine (2%) and dexamethasone (5 mg, 1 mL). The drug was injected directly and infiltrated into the abnormal tissue. Ultrasonic guidance was used for injection of deep lesions. The drug dose, drug concentration, and treatment interval was adjusted according to the lesional size, location, classification, and response to therapy. Dexamethasone was used to reduce the possibility of allergic reaction caused by bleomycin A5. Repeat injections were typically performed at 2 to 3 week intervals.

Fig 1. Microcystic lymphatic malformation (LM) in the tongue. **A,** Before treatment. **B,** After four bleomycin A5 injections.

Clinical manifestations, imaging characteristics, and therapeutic outcomes were reviewed. The results were assessed by a panel of three independently based oral surgeons who were given data from the clinical follow-up, photographs, and Doppler ultrasonography scans. The three oral surgeons directly examined the patients, and measured and calculated lesion size. Only two post-treatment lesions (the lesions located on the surface of the oral mucosa) were evaluated by photographs because the patients could not come to the clinic. A flexible tape was used to measure maximal length and width above the visible or palpable lesion surface. Lesion size was estimated by calculating its surface area. For the deep lesions, the lesion size was evaluated by the 2-dimensional scanning of Doppler ultrasonography scan. The area of the lesion was calculated by the maximal length and width. The response rate was graded as follows: reduction greater than 90%, reduction of 50% to 90%, and reduction less than 50%. The

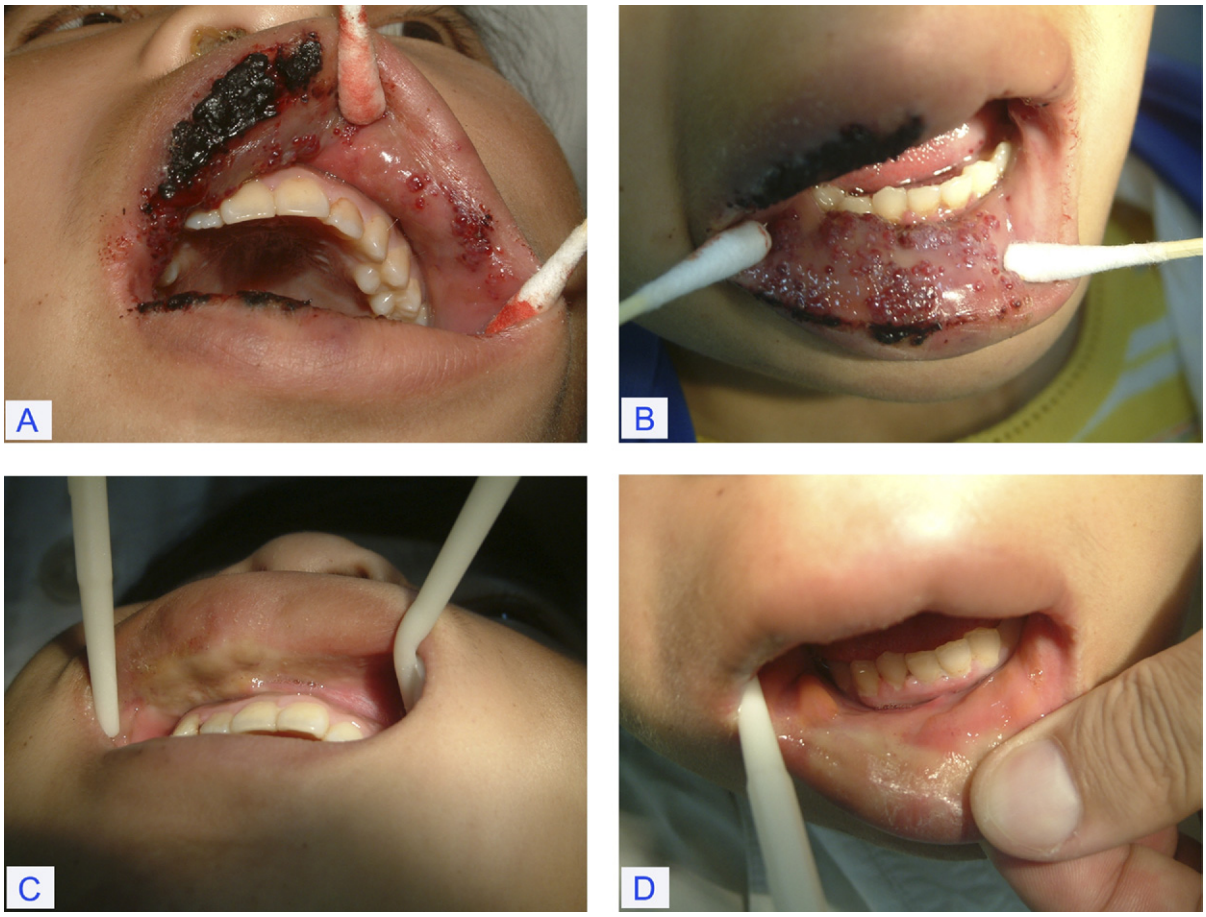

Fig 2. Microcystic lymphatic malformation (LM) in the upper and lower lips. **A** and **B,** Before treatment. **C** and **D,** After six bleomycin A5 injections.

follow-up time was 6 months to 3 years after the last treatment and the mean follow-up time was 16 months.

RESULTS

Of the 65 patients, 41 were men and 24 were women (1.7:1 male:female ratio), the age range was 3 months to 45 years (mean, 12 years). Thirty-two lesions (49%) were macrocystic, 30 (46%) were microcystic, and 3 (5%) were combined. Anatomic areas involved by LM are summarized in Table I. The size of the lesions treated by sclerotherapy was 5.4 to 103.7 cm^2 (mean, 19.2 cm^2). Each patient received 1 to 10 injections (mean, 3.0 injections) for the whole course of treatment. Total dose of bleomycin A5 administered was 8 to 80 milligrams (mean, 24 mg).

The outcome in typical cases is shown in Figs 1 to 4. Results were classified by cystic morphology of the LMs (Table II). Macrocystic LMs exhibited the most shrinkage.

The complications included ulceration of oral mucosa (n = 4), slight soft tissue atrophy (n = 1), mild fever (n = 2), and hematoma (n = 1). Transient complications were mainly swelling and pain. There were no allergic reactions, pulmonary fibrosis, nerve injury, or other complications during or after the course of treatment. There was no recurrence throughout the follow-up period.

DISCUSSION

LMs are present at birth but are not always obvious. Most become evident before 2 years of age. LMs occur in any part of the body, but are most commonly seen in lymphatic dense areas, such as the cervicofacial region, axilla/chest, mediastinum, retroperitoneum, buttock, and anogenital region.[1] Typical lesions in the superficial oral mucosa manifest as multiple fluid-filled and tiny clear or red vesicles. The lesions usually involve the surface of the oral mucosa or submucosal area but do not involve the muscles and subcutaneous tissue. Extensive and deep involvement of lingual LM is the common cause of macroglossia. Cutaneous vesicles rarely occur in facial skin. The extensive macrocystic and microcystic LMs involving deep dermal and subcutaneous tissue can result in remarkable cervicofacial deformity caused by thickening and swelling of adjacent tissue.

Surgical excision has been the traditional approach for LMs.[4-6] The results are good for LMs that are macrocystic and well demarcated. The outcome after resection of exten-

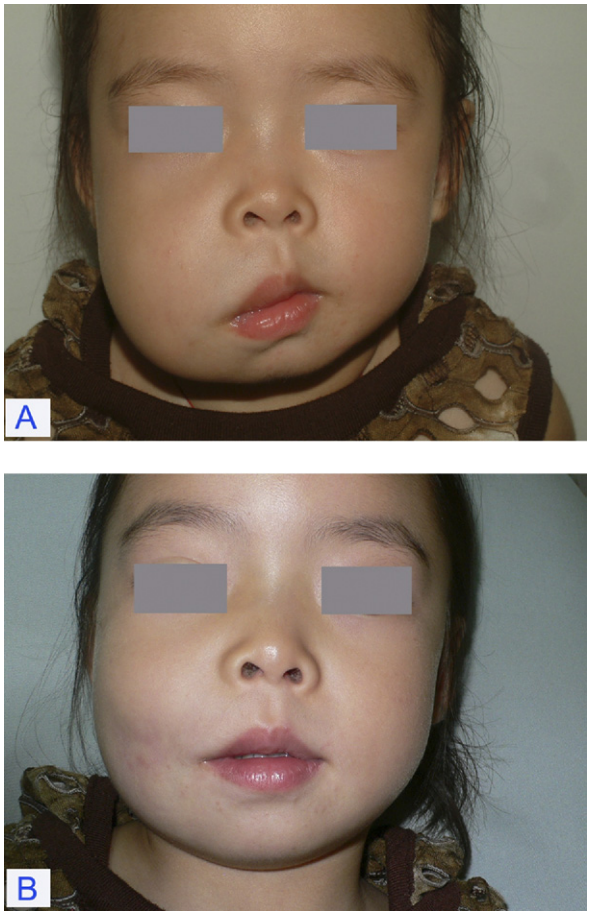

Fig 3. Microcystic lymphatic malformation (LM) in the cheek involving both buccal mucosa and deep tissue. **A,** Before treatment. **B,** After four bleomycin A5 injections.

sive macrocystic and diffuse microcystic lesions is often disappointing. These large lesions are frequently poorly defined without distinct tissue planes between the abnormal and normal structures. Therefore, it is usually impossible to precisely dissect and completely resect these lesions. Severe edema in the oral floor and parapharyngeal region can follow attempts at surgical excision of an extensive macrocystic LM, resulting in airway obstruction and asphyxia.

Problems after resection of LMs have prompted exploration of nonsurgical therapies. A laser has been used for cutaneous and mucosal lesions[8,9]; however, the recurrence rate is relatively high. Recently, radiofrequency ablation has been successfully used for the control of microcystic LMs in the oral cavity.[10,11,22] This technique is safe and relatively effective, but further studies are needed to assess long-term control.

Sclerotherapy is considered to be the most effective treatment of LMs. Various sclerosing agents have been used (eg, alcoholic solution of zein,[17] fibrin sealant,[18] 3% sodium tetradecyl sulfate,[2] and acetic acid).[19] Doxycycline is extensively used in the United States for macrocystic

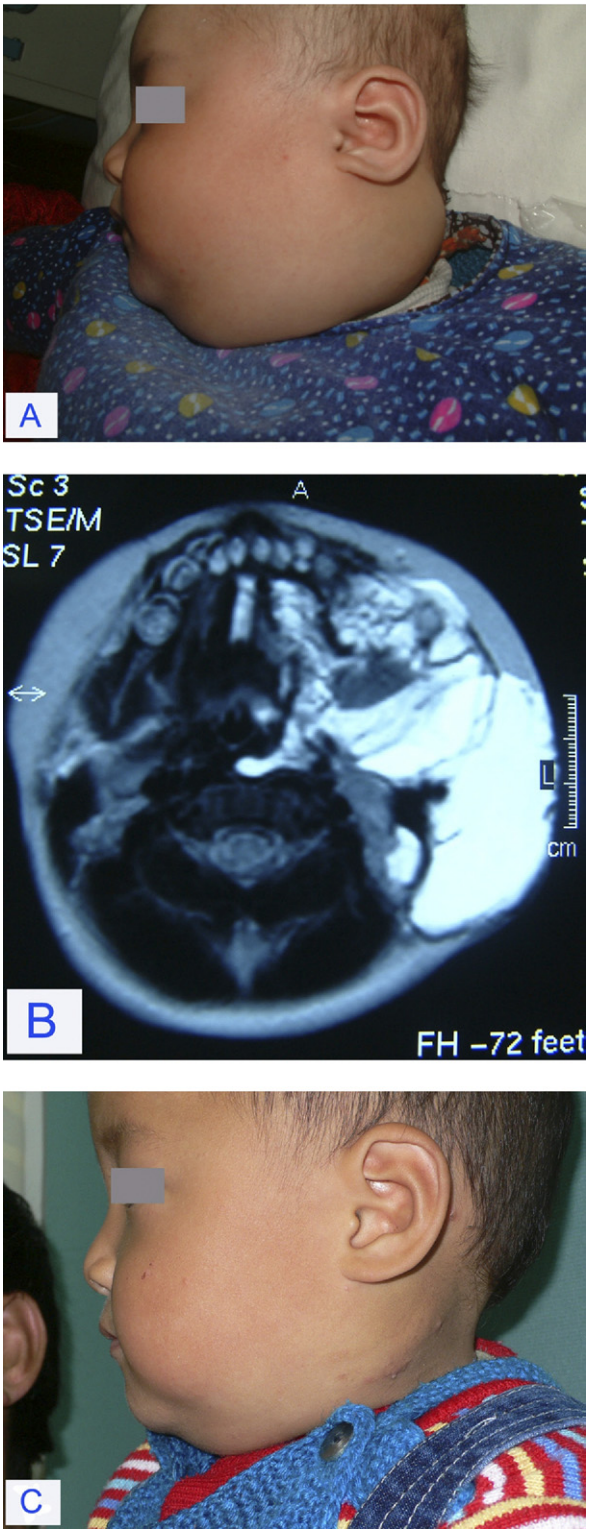

Fig 4. Macrocystic lymphatic malformation (LM) involving submandibular, upper neck, and parotid areas. **A,** Before treatment. **B,** T2-weighted magnetic resonance imaging on axial plane showing a multiloculated high intensity signal. **C,** After four bleomycin A5 injections.

Table II. Treatment response to bleomycin A5 injections

LM type	*Size reduction*		
	Greater than 90% n = (%)	*50% to 90% n = (%)*	*Less than 50% n = (%)*
Macrocystic	26 (81)	6 (19)	
Microcystic	19 (63)	10 (33)	1 (4)
Combined	2 (67)		1 (33)
Total	47 (72)	16 (25)	2 (3)

LM, Lymphatic malformation.

lesions[16,23]; however, more studies are needed to show possible efficacy for microcystic LMs. OK-432 was introduced by Ogita et al[12] in 1987 and is also a commonly used sclerosing agent. It consists of bacterial components of an avirulent strain of group A streptococcus pyogenes. Injection of OK-432 can cause endothelial damage/death and shrinkage of LMs. OK-432 has shown good to excellent responses in the majority of patients[13]; however, other reports have shown that microcystic LMs respond poorly or not at all to OK-432.[24-26]

Bleomycin is another agent for sclerotherapy, especially for macrocystic LMs.[14,15,27,28] Okada et al[29] studied tissues in patients who were given bleomycin injections preoperatively, and found the absence of normal lymphatic epithelial lining, prominent infiltration of lymphocytes, other inflammatory cells, and marked proliferation of stromal connective tissue. Pingyangmycin is a similar compound isolated from *Streptomyces pingyangensisn* cultures,[30] the major active component of which is bleomycin A5. Bleomycin A5 is often used in China for treatment of squamous cell carcinoma, and for venous malformations[31] and LMs.[32,33]

We found that intralesional bleomycin A5 was reasonably effective in shrinking both macrocystic and microcystic LMs. More than 81% of the macrocystic lesions and nearly 63% of the microcystic lesions exhibited greater than 90% size reduction. In the past, bleomycin injection was mostly used for treatment of macrocystic LMs. We also noted that part of the microcystic LMs, especially if involving superficial oral mucosa had a favorable response to bleomycin A5. All of the oral mucosal lesions disappeared after sclerotherapy. Only 2 of the 65 lesions responded poorly to the treatment with less than 50% reduction. One patient had a diffuse bilateral microcystic lesion involving the submental and submandibular region, and the other had combined LM with predominantly microcystic lesions involving the tongue, bilateral cheek, and right submandibular region. The common characteristics of these 2 patients are that they both had diffuse microcystic lesions involving contiguous anatomic areas and deep tissue. For the 2 patients, we plan to give partial resection and then sclerotherapy later. The procedures may be repeated several times.

Based on the results in our patients, we recommend bleomycin A5 injection as the first-line therapy for most macrocystic LMs. We also use bleomycin A5 injection as the primary treatment for the superficial oral mucosa LM. Some lesions are scarred due to the repeated infection. For this type of lesion, it is difficult to aspirate the lymphatic fluid from the lesion and inject the sclerosing agent into the intraluminal space of the lesion. The drug is injected directly and infiltrates into the area of abnormal tissue. The injection must be at high pressure until the surface turns pale and rupture of the vesicles can be seen. There is always concern about extravasation of a sclerosant and possible damage to adjacent tissue. Oral mucosal ulceration occurred in 4 patients, but the lesions disappeared completely after healing of the ulceration.

Some relatively localized deep microcystic lesions involving the lips or cheeks also responded well to the bleomycin A5 injection. The possible complication is soft tissue atrophy; 1 patient in our series had minor atrophy of the upper lip. The appropriate drug dosage and concentration should be used when injecting labial lesions. For the children with microcystic LMs lesions in the lips, we suggest the lower dosage, lower concentration, and longer intervals between injections. For instance, bleomycin A5 (8 mg) powder is dissolved in 5 mL of lidocaine (2%) and dexamethasone (5 mg, 1 mL). The drug dosage was less than 5 mg for every injection. The interval time was extended to 1 to 2 months.

Bleomycin A5 sclerotherapy was also useful for residual unresectable lesions. Five of 65 patients first underwent partial surgical resection, and then bleomycin A5 sclerotherapy. The injection of bleomycin A5 near the facial nerve did not cause injury. The total dose of bleomycin administered to the patients is of concern. Excessive use of large doses of bleomycin A5 may increase the risk of pulmonary fibrosis. Partial surgical resection can reduce the volume of the lesions, and as a result, reduce the dose of sclerosing agent needed. This combined approach is of major benefit to patients with a large diffuse LM that will require a large dose of sclerosing agent to accomplish the whole course of treatment.

There are several options for the treatment of extensive LMs in our department: partial resection and then sclerotherapy, sclerotherapy first and then surgical resection, and repeated sclerotherapy and surgical resection. It mainly depends on the patients' age, and the location, size, and type of the lesions. In the current series, the main purpose was to evaluate the effects of bleomycin A5 sclerotherapy for LMs and incompletely resected LMs, so we did not choose the patients with sclerotherapy first and then surgical resection. That did not mean we suggested that every patient underwent partial resection first and then injection of bleomycin A5. We believed that the sclerosing agent was injected first and then surgical resection was a good option for some lesions.

Previously reported complications of intralesional bleomycin A5 include fever, ulceration, anorexia, vomiting, and cellulitis.[27,29,32,33] Pulmonary fibrosis occasionally arises in the patients after administration of a large dose, such as needed for patients with a malignant tumor.[34] Hypersensitivity reactions are rare, but are potentially fatal.[35] We used 5 mg dexamethasone with each bleomycin A5 injection to prevent possible allergic reaction. In our series, besides ulceration of oral mucosa and soft tissue atrophy, the other complica-

tions were mild fever in 2 patients and hematoma in 1 patient with upper neck and parotid macrocystic LM.

CONCLUSIONS

These data suggest intralesional injection of bleomycin A5 is safe and effective for the treatment of macrocystic LMs, superficial oral mucosal LMs, and relatively localized deep microcystic lesions. For the extensive macrocystic LMs involving multiple anatomic areas and diffuse microcystic lesions involving deep tissue, bleomycin A5 injection combined with surgical excision is recommended.

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AUTHOR CONTRIBUTIONS

Conception and design: YY, MS, DL
Analysis and interpretation: YY, MS
Data collection: YY, QM, XC, JA, LT, LW
Writing the article: YY
Critical revision of the article: YY, MS, QM, DL
Final approval of the article: YY
Statistical analysis: YY, LT, LW
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Overall responsibility: YY

REFERENCES

1. Mulliken JB, Fishman SJ, Burrows PE. Vascular anomalies. Curr Probl Surg 2000;37:517-84.
2. Alomari AI, Karian VE, Lord DJ, Padua HM, Burrows PE. Percutaneous sclerotherapy for lymphatic malformations: a retrospective analysis of patient-evaluated improvement. J Vasc Interv Radiol 2006;17:1639-48.
3. Perkins JA, Maniglia C, Magit A, Sidhu M, Manning SC, Chen EY. Clinical and radiographic findings in children with spontaneous lymphatic malformation regression. Otolaryngol Head Neck Surg 2008; 138:772-7.
4. Lei ZM, Huang XX, Sun ZJ, Zhang WF, Zhao YF. Surgery of lymphatic malformations in oral and cervicofacial regions in children. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;104:338-44.
5. Padwa BL, Hayward PG, Ferraro NF, Mulliken JB. Cervicofacial lymphatic malformation: clinical course, surgical intervention, and pathogenesis of skeletal hypertrophy. Plast Reconstr Surg 1995;95:951-60.
6. Lille ST, Rand RP, Tapper D, Gruss JS. The surgical management of giant cervicofacial lymphatic malformations. J Pediatr Surg 1996;31: 1648-50.
7. Acevedo JL, Shah RK, Brietzke SE. Nonsurgical therapies for lymphangiomas: a systematic review. Otolaryngol Head Neck Surg 2008; 138:418-24.
8. Wang LC, Krunic AL, Medenica MM, Soltani K, Busbey S. Treatment of hemorrhagic lymphatic malformation of the tongue with a pulsed-dye laser. J Am Acad Dermatol 2005;52:1088-90.
9. Berwald C, Salazard B, Casanova D, Bardot J, Magalon G. [Indications of lasers treatment for lymphatic malformations.] [Article in French] Ann Chir Plast Esthet 2006;51:429-32.
10. Leboulanger N, Roger G, Caze A, Enjolras O, Denoyelle F, Garabedian EN. Utility of radiofrequency ablation for haemorrhagic lingual lymphangioma. Int J Pediatr Otorhinolaryngol 2008;72:953-8.
11. Ryu NG, Park SK, Jeong HS. Low power radiofrequency ablation for symptomatic microcystic lymphatic malformation of the tongue. Int J Pediatr Otorhinolaryngol 2008;72:1731-4.
12. Ogita S, Tsuto T, Tokiwa K, Takahashi T. Intracystic injection of OK-432: a new sclerosing therapy for cystic hygroma in children. Br J Surg 1987;74:690-1.
13. Yoo JC, Ahn Y, Lim YS, Hah JH, Kwon TK, Sung MW, et al. OK-432 sclerotherapy in head and neck lymphangiomas: long-term follow-up result. Otolaryngol Head Neck Surg 2009;140:120-3.
14. Yura J, Hashimoto T, Tsuruga N, Shibata K. Bleomycin treatment for cystic hygroma in children. Nippon Geka Hokan 1977;46:607-14.
15. Mathur NN, Rana I, Bothra R, Dhawan R, Kathuria G, Pradhan T. Bleomycin sclerotherapy in congenital lymphatic and vascular malformations of head and neck. Int J Pediatr Otorhinolaryngol 2005;69:75-80.
16. Nehra D, Jacobson L, Barnes P, Mallory B, Albanese CT, Sylvester KG. Doxycycline sclerotherapy as primary treatment of head and neck lymphatic malformations in children. J Pediatr Surg 2008;43:451-60.
17. Emran MA, Dubois J, Laberge L, Al-Jazaeri A, Bütter A, Yazbeck S. Alcoholic solution of zein (Ethibloc) sclerotherapy for treatment of lymphangiomas in children. J Pediatr Surg 2006;41:975-9.
18. Castañón M, Margarit J, Carrasco R, Vancells M, Albert A, Morales L. Long-term follow-up of nineteen cystic lymphangiomas treated with fibrin sealant. J Pediatr Surg 1999;34:1276-9.
19. Won JH, Kim BM, Kim CH, Park SW, Kim MD. Percutaneous sclerotherapy of lymphangiomas with acetic acid. J Vasc Interv Radiol 2004; 15:595-600.
20. Umezawa H, Maeda K, Takeuchi T, Okami Y. New antibiotics, bleomycin A and B. J Antibiot (Tokyo) 1966;19:200-9.
21. Umezawa H. Recent study on biochemistry and action of bleomycin. In: Carter SK, Crook ST, Umezawa H, editors. Bleomycin: current status and new developments. New York:Academic Press 1978. pp 15-20.
22. Grimmer JF, Mulliken JB, Burrows PE, Rahbar R. Radiofrequency ablation of microcystic lymphatic malformation in the oral cavity. Arch Otolaryngol Head Neck Surg 2006;132:1251-6.
23. Cordes BM, Seidel FG, Sulek M, Giannoni CM, Friedman EM. Doxycycline sclerotherapy as the primary treatment for head and neck lymphatic malformations. Otolaryngol Head Neck Surg 2007;137:962-4.
24. Luzzatto C, Lo Piccolo R, Fascetti Leon F, Zanon GF, Toffolutti T, Tregnaghi A. Further experience with OK-432 for lymphangiomas. Pediatr Surg Int 2005;21:969-72.
25. Banieghbal B, Davies MR. Guidelines for the successful treatment of lymphangioma with OK-432. Eur J Pediatr Surg 2003;13:103-7.
26. Okazaki T, Iwatani S, Yanai T, Kobayashi H, Kato Y, Marusasa T, et al. Treatment of lymphangioma in children: our experience of 128 cases. J Pediatr Surg 2007;42:386-9.
27. Orford J, Barker A, Thonell S, King P, Murphy J. Bleomycin therapy for cystic hygroma. J Pediatr Surg 1995;30:1282-7.
28. Baskin D, Tander B, Bankaoğlu M. Local bleomycin injection in the treatment of lymphangioma. Eur J Pediatr Surg 2005;15:383-6.
29. Okada A, Kubota A, Fukuzawa M, Imura K, Kamata S. Injection of bleomycin as a primary therapy of cystic lymphangioma. J Pediatr Surg 1992;27:440-3.
30. Tai KW, Chou MY, Hu CC, Yang JJ, Chang YC. Induction of apoptosis in KB cells by pingyangmycin. Oral Oncol 2000;36:242-7.
31. Yang Y, Sun M, Hou R, Yan Z, Wang L, Cheng X, et al. Preliminary study of fibrin glue combined with pingyangmycin for the treatment of venous malformations in the oral and maxillofacial region. J Oral Maxillofac Surg 2008;66:2219-25.
32. Zhong PQ, Zhi FX, Li R, Xue JL, Shu GY. Long-term results of intratumorous bleomycin-A5 injection for head and neck lymphangioma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;86: 139-44.
33. Bai Y, Jia J, Huang XX, Alsharif MJ, Zhao JH, Zhao YF. Sclerotherapy of microcystic lymphatic malformations in oral and facial regions. J Oral Maxillofac Surg 2009;67:251-6.
34. Zhao FY. [The efficacy and side effects of the preoperative administration of pingyangmycin in squamous cell carcinoma of the oromaxillo-facial region.] [Article in Chinese] Zhonghua Kou Qiang Ke Za Zhi 1985;20:150-3.
35. Lam MS. The need for routine bleomycin test dosing in the 21st century. Ann Pharmacother 2005;39:1897-902.

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